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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,462	10/21/2003	James P. Snyder	007157/270549	4831

826 7590 02/25/2005

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,462	SNYDER ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response filed on 12/07/2004 is made of record. In view of the second preliminary amendment, the restriction requirement made in the previous office action is withdrawn. Claims 13-38 are pending.

Priority

The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ 2d 1077 (Fed. Cir. 1994).

In the instant case the provisional application dose not provide support for all subject matter embraced in the instant application. Hence, the priority to provisional application is not granted for examination of the instant application.

Information Disclosure Statement

References cited in the Information Disclosure Statement , filed on 5/17/2004, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Following apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim and share the same limitation.

1. Recitation of " and pharmaceutically acceptable salts thereof" in claims 1, 21, 26 and 34 renders these claims and their dependent claims indefinite as it is not clear whether the claim is compound claim or composition claim with above said limitations. Note Markush recitation should be in alternate form and in singular. Replacement of "and" with "or" and "salts" with "salt" is suggested.

2. Recitation of "carboxylic acid, carboxylic ester, carboxamide" in claims 1, 21, 26 and 34 in definition of X_1 and X_2 renders these claims indefinite as it is not clear what is intended. Note these are compounds as recited not groups. Further more the scope of carboxylic acid is not clear. As recited it can include any organic compound. An appropriate correction is needed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-34 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating breast cancer and human melanoma, does not reasonably provide enablement for treating any or all cancer. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above.

The instant claims are drawn to "treating cancerous tissue" in general. The scope of the claims includes any or all cancer due to VEGF/TF inhibition activity including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various cancers which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 42-52. The instant compounds are disclosed to have VEGF/TF inhibition activity and it is recited that the instant compounds are therefore useful in treating any or all cancer stated above for which applicants provide no competent evidence. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most cancers , are very difficult to treat and despite the fact that there are many drugs including those cited in the specification, which can be used for same VEGF/TF inhibition activity.

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the any or all cancer embraced by the terms cancerous tissue.

Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Chen et al. Thromb. Haemost. 86(1): 334-345, 2001.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors

include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require VEGF/TF inhibition activity.

2) The state of the prior art: A very recent publication expressed that the VEGF/TF inhibition activity effects are unpredictable and are still exploratory. See Chen et al cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all cancerous tissue and the state of the art is that the effects of VEGF/TF inhibition activity are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all proliferative diseases and cancers including those yet to be related to VEGF/TF inhibition activity .

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 13-15, 19-20 , 22-23, 25-28, 30, 32-33 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by El-Subbagh et al. J. Med. Chem. 43: 2915-2921, 2000.

El-Subbagh et al. teaches several compounds, which include generically compounds, composition and the method of use claimed in the instant claims. See entire document especially see formula 13.

Claims 13, 17-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Desiraju et al. et al. Indian Journal of Chemistry. 27B(10): 953-954, 1988. CAPLUS Abstract provided.

See compound shown on page 17 of CAPLUS Abstract.

Claims 13, 17-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Druker et al. US 3,515,559.

See column 2 for various pyridilidine cycloalkanones.

Claims 13-15, 18-20 and 21-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Krapcho et al. US 3,852,279.

See example 13 on column 8.

Claims 13, 17-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Katritzky et al. Journal of Heterocyclic Chemistry 25(5), 1321-1325. CAPLUS Abstract provided.

See compounds shown in pages 18-19 of CAPLUS Abstract.

Claims 13-15 and19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Gutkowska Akad. Poloniae Pharmaceutica , 30(4), 361-364, 1973. CAPLUS Abstract provided.

See compounds shown in pages 25-26 of CAPLUS Abstract.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM.

The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (571) 272-0674. If Applicants are unable to reach Mukund Shah within 24-hour period, they may contact James O. Wilson, Acting-SPE of art unit 1624 at 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Venkataraman Balasubramanian

Venkataraman Balasubramanian

2/21/2005